



## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

<b>(51) International Patent Classification 7 :</b> C07D 243/16, 243/20, 243/22, 243/24, 401/04, 401/12, 403/12, 487/04, A61K 31/55 // (C07D 401/04, 243:00, 213:00) (C07D 401/12, 243:00, 213:00) (C07D 487/04, 243:00, 235:00)		<b>A1</b>	<b>(11) International Publication Number:</b> WO 00/69836 <b>(43) International Publication Date:</b> 23 November 2000 (23.11.00)
<b>(21) International Application Number:</b> PCT/US00/13134 <b>(22) International Filing Date:</b> 12 May 2000 (12.05.00) <b>(30) Priority Data:</b> 9911152.8 14 May 1999 (14.05.99) GB <b>(63) Related by Continuation (CON) or Continuation-in-Part (CIP) to Earlier Application</b> US 9911152.8 (CIP) Filed on 14 May 1999 (14.05.99) <b>(71) Applicant (for all designated States except US):</b> GLAXO GROUP LIMITED [GB/GB]; Glaxo Wellcome House, Berkeley Avenue, Greenford, Middlesex UB6 0NN (GB). <b>(72) Inventors; and</b> <b>(75) Inventors/Applicants (for US only):</b> FELDMAN, Paul, L. [US/US]; Glaxo Wellcome Inc., Five Moore Drive, P.O. Box 13398, Research Triangle Park, NC 27709 (US). JUNG, David, Kendall [US/US]; Glaxo Wellcome Inc., Five Moore Drive, P.O. Box 13398, Research Triangle Park, NC 27709 (US). KALDOR, Istvan [HU/US]; Glaxo Wellcome Inc., Five Moore Drive, P.O. Box 13398, Research Triangle Park, NC 27709 (US). PACOFSKY, Gregory, J. [US/US]; Glaxo Wellcome Inc., Five Moore Drive, P.O. Box 13398, Research Triangle Park, NC 27709 (US). STAFFORD, Jeffrey, A. [US/US]; Glaxo Wellcome Inc., Five Moore Drive, P.O. Box 13398, Research Triangle Park, NC 27709 (US). TIDWELL, Jeffrey, H. [US/US]; Glaxo Wellcome Inc., Five Moore Drive, P.O. Box 13398, Research Triangle Park, NC 27709 (US). <b>(74) Agents:</b> LEVY, David, J.; Glaxo Wellcome Inc., Five Moore Drive, P.O. Box 13398, Research Triangle Park, NC 27709-3398 (US) et al. <b>(81) Designated States:</b> AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG). <b>Published</b> <i>With international search report.</i> <i>Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>			
<b>(54) Title:</b> SHORT-ACTING BENZODIAZEPINES			
<b>(57) Abstract</b> <p>It has now been found that compounds of the present invention as described in Benzodiazepine derivatives of Formula (I) containing a carboxylic ester moiety and thereby capable of being inactivated by nonspecific tissue esterases in an organ-independent elimination mechanism and thereby providing a more predictable and reproducible pharmacodynamic profile. The compounds of the present invention are suitable for therapeutic purposes, including sedative-hypnotic, anxiolytic, muscle relaxant and anticonvulsant purposes and are useful to be administered intravenously in the following clinical settings: preoperative sedation, anxiolysis, and amnestic use for perioperative events; conscious sedation during short diagnostic, operative or endoscopic procedures; as a component for the induction and maintenance of general anesthesia, prior and/or concomitant to the administration of other anesthetic agents; ICU sedation.</p>			

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## INTERNATIONAL SEARCH REPORT

Int. Application No

PCT/US 00/13134

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07D243/16 C07D243/20 C07D243/22 C07D243/24 C07D401/04  
 C07D401/12 C07D403/12 C07D487/04 A61K31/55  
 //(C07D401/04,243:00,213:00),(C07D401/12,243:00,213:00),

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, PAJ, CHEM ABS Data, WPI Data

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 881 235 A (CENTRE NAT RECH SCIENT ;SOD CONSEILS RECH APPLIC (FR)) 2 December 1998 (1998-12-02) example 3B5	1
X	WO 98 00405 A (LYNCH JOSEPH J JR ;MERCK & CO INC (US); SALATA JOSEPH J (US)) 8 January 1998 (1998-01-08) scheme 9, examples 65,66,98,107	1,21-23



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

## \* Special categories of cited documents :

- \*A\* document defining the general state of the art which is not considered to be of particular relevance
- \*E\* earlier document but published on or after the international filing date
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- \*O\* document referring to an oral disclosure, use, exhibition or other means
- \*P\* document published prior to the international filing date but later than the priority date claimed

\*T\* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

\*X\* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

\*Y\* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

\*&\* document member of the same patent family

Date of the actual completion of the international search

28 August 2000

Date of mailing of the international search report

26/09/2000

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# INTERNATIONAL SEARCH REPORT

Int. Application No.

PCT/US 00/13134

**A. CLASSIFICATION OF SUBJECT MATTER**  
IPC 7 (C07D487/04, 243:00, 235:00)

According to International Patent Classification (IPC) or to both national classification and IPC

**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>DATABASE CHEMABS 'Online! CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; ICHIHARA, MASATO ET AL: "Preparation of diazepine derivatives as specific inhibitors of human renin" retrieved from STN Database accession no. 124:232494 CA XP002145751 RNs 174399-19-0, 174399-20-3, 174399-21-4, 174399- 22-5, 174399-23-6, 174399-24-7, 174399-26-9, 174399-28-1, 174399-29-2, 174399-30-5 &amp; JP 07 304755 A (YAMANOUCI PHARMA CO LTD, JAPAN) 21 November 1995 (1995-11-21)</p> <p style="text-align: center;">--- -/-</p>	1, 21-23

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

\* Special categories of cited documents :

- \*A\* document defining the general state of the art which is not considered to be of particular relevance
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- \*T\* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- \*X\* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- \*Y\* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- \*8\* document member of the same patent family

Date of the actual completion of the international search

28 August 2000

Date of mailing of the international search report

Name and mailing address of the ISA

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Frelon, D

## INTERNATIONAL SEARCH REPORT

Int. Application No.

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## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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X	EP 0 264 797 A (ABBOTT LAB) 27 April 1988 (1988-04-27) figures 11,23 ---	1
X	GOUMRI-MAGNET S ET AL: "FREE AND SUPPORTRED PHOSPHORUS YLIDES AS STRONG NEUTRAL BRONSTED BASES" JOURNAL OF ORGANIC CHEMISTRY, US, AMERICAN CHEMICAL SOCIETY. EASTON, vol. 64, no. 10, 14 May 1999 (1999-05-14), pages 3741-3744, XP000825802 ISSN: 0022-3263 example 7F ---	1
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Int. Application No

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## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DATABASE CHEMABS 'Online! CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; BOCK, MARK G. ET AL: "Curtius rearrangement in the 5-phenyl-1,4-benzodiazepine series. Unprecedented participation by an imine nitrogen" retrieved from STN Database accession no. 113:171988 XP002145753 RN 129479-01-5 & J. HETEROCYCL. CHEM. (1990), 27(3), 631-6 ,	1
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PCT/US 00/13134

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

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Int. Application No.

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## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	FR 2 115 265 A (CIBA GEIGY AG) 7 July 1972 (1972-07-07) page 2; claims	1-30
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Information on patent family members

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# PATENT COOPERATION TREATY

## PCT

### INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference <b>PU3318WO</b>	<b>FOR FURTHER ACTION</b>		See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. <b>PCT/US00/13134</b>	International filing date (day/month/year) <b>12/05/2000</b>	Priority date (day/month/year) <b>14/05/1999</b>	
International Patent Classification (IPC) or national classification and IPC <b>C07D243/16</b>			
Applicant <b>GLAXO GROUP LIMITED et al.</b>			


1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.
  
2. This REPORT consists of a total of 9 sheets, including this cover sheet.
 

☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of    sheets.

3. This report contains indications relating to the following items:

- I    ☒ Basis of the report
- II   ☐ Priority
- III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV   ☐ Lack of unity of invention
- V    ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI   ☐ Certain documents cited
- VII ☒ Certain defects in the international application
- VIII ☒ Certain observations on the international application

Date of submission of the demand  <b>21/11/2000</b>	Date of completion of this report  <b>27.07.2001</b>
Name and mailing address of the international preliminary examining authority:   European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer  <b>Usuelli, A</b>  Telephone No. +49 89 2399 7366



**EXPRESS MAIL NO.**  
**EL395943235US**

# INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/US00/13134

## I. Basis of the report

1. With regard to the **elements** of the international application (*Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17)*):

**Description, pages:**

1-75 as originally filed

**Claims, No.:**

1-30 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

# INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/US00/13134

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

### III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application.

☒ claims Nos. 24-26.

because:

☒ the said international application, or the said claims Nos. 24-26 relate to the following subject matter which does not require an international preliminary examination (*specify*):  
**see separate sheet**

☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the said claims Nos. .

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

☐ the written form has not been furnished or does not comply with the standard.

☐ the computer readable form has not been furnished or does not comply with the standard.

### V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	4-20, 22, 23, 25-30
	No:	Claims	1-3,21,24

Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-30

Industrial applicability (IA)	Yes:	Claims	1-23, 27-30
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**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT**

International application No. PCT/US00/13134

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No: Claims

2. Citations and explanations  
**see separate sheet**

**VII. Certain defects in the international application**

The following defects in the form or contents of the international application have been noted:  
**see separate sheet**

**VIII. Certain observations on the international application**

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:  
**see separate sheet**

**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT - SEPARATE SHEET**

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International application No. PCT/US00/13134

**Re Item III**

**Non-establishment of opinion with regard to novelty, inventive step and industrial applicability**

For the assessment of the present claims 24-26 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

**Re Item V**

**Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

1- Reference is made to the following documents:

D1: EP 0 881 235 A

D2: WO 98 00405 A

D3: DATABASE CHEMABS [Online] CHEMICAL ABSTRACTS SERVICE, accession no. 124:232494 CA XP002145751 & JP 07 304755 A

D4: EP 0 508 798 A

D5: EP 0 264 797 A

D6: JOURNAL OF ORGANIC CHEMISTRY, US, AMERICAN CHEMICAL SOCIETY. EASTON, vol. 64, no. 10, 14 May 1999 (1999-05-14), pages 3741-3744, XP000825802

D7: DATABASE CHEMABS [Online] CHEMICAL ABSTRACTS SERVICE, accession no. 129:275897 XP002145752 & HELV. CHIM. ACTA (1998), 81(8), 1567-1582

D8: J. CHEM. SOC., PERKIN TRANS. 2 (1998), (3), 547-559, XP002145750

D9: HETEROCYCL. CHEM. (1990), 27(3), 631-6

D10: DATABASE CHEMABS [Online] CHEMICAL ABSTRACTS SERVICE, accession no. 82:156233 XP002145754 & BOLL. CHIM. FARM. (1974), 113(12), 642-4

D11: DATABASE CHEMABS [Online] CHEMICAL ABSTRACTS SERVICE, accession no. 80:105318 XP002145755 & J. CHEM. SOC., CHEM. COMMUN. (1973), (19), 721-2

**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT - SEPARATE SHEET**

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International application No. PCT/US00/13134

D12: DATABASE CHEMABS [Online] CHEMICAL ABSTRACTS SERVICE, Database accession no. 79:137109 XP002145756 & J. ORG. CHEM. (1973), 38(20), 3502-7

D13: DATABASE CHEMABS [Online] CHEMICAL ABSTRACTS SERVICE, accession no. 73:64862 XP002145757 & TAKEDA KENKYUSHO HO (1970), 29(1), 134-4

D14: EP 0 122 889 A

D15: FR 2 414 043 A

D16: CH 608 234 A

D17: FR 2 231 385 A

D18: FR 2 183 716 A

D19: EP 0 100 906 A

D20: FR 2 115 265 A

D21: FR 2 034 577 A

## 2- Novelty

Several documents of the prior art disclose specific compounds or general formulas which are encompassed by the present formula (I)(1) (compounds of formula (I) where R5 and R6 together represent an O or S atom). Hereafter are briefly indicated the major defects of the application concerning the issue of novelty. In the most part of cases the documents affect the novelty of claims 1 and 2. D2 affects also the novelty of claim 21 which relates to pharmaceutical compositions. D10 and D11 are relevant also in respect of claims 21 and 3.

- the compound 3b5 page 9 of D1 is encompassed by present claims 1-2
- present formula (I)(1) is at least in part encompassed by the formula (I) of D2. Specific examples are given on schema 9,12,14 and examples 53,54,65,66,98
- D3: all the specific examples
- D4: compound (4) of page 8, example 2a
- D5: fig. 11,23
- D6: compound 7f
- D7: the compound 19 is excluded from the present claims for the effect of the disclaimer
- D8: the compounds 3f-h are excluded from the present claims for the effect of the disclaimer
- D9: compound 11

**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT - SEPARATE SHEET**

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International application No. PCT/US00/13134

- D10: compound 1a
- D11: compound 8
- D12: compound 4
- D13: single example given

In view of these disclosures claims 1-3, 21 and 24 lack of novelty in the sense of Article 33.2 PCT.

### 3- Inventive Step

3.1- D3 discloses the effect of certain benzodiazepin-2-ones on the central nervous system. Other benzodiazepin-2 one derivatives active on the CNS are disclosed in D13-D16. These compounds can be used for example as anxiolytic, narcotic, hypnotic or analgesic agents. All these documents can be regarded as the closest prior art in respect of those parts of the formula (I)(1) rendered novel by opportune delimitation from D1-D13.

D3 and D13 clearly indicate the potential use of the compounds of formula (I)(1) as CNS agents, for example as anaesthetic or analgesic. Compounds having a similar activity are disclosed also in D14-D15. The compounds of formula (I)(1) differ from the compounds of these two documents mainly for the substitution in position 3. In particular the compounds of D15 differ from the compounds of the invention only in that they lack the group X which can be, for instance, a CH<sub>2</sub> radical. In view of these disclosures it appears that the skilled person faced with the problem of providing alternative agents for the treatment of the diseases indicated in claims 24-26 would consider obvious to prepare the benzodiazepin-2-one of formula (I)(1) since they are similar or identical to the compounds of the prior art having the same activity. Accordingly it is considered that only in presence of unexpected effect which should be demonstrated by means of comparative tests vis-à-vis of the compounds representing the closest prior art, the compounds of formula (I)(1) could be considered inventive. However, considering that many benzodiazepin-2-one derivatives having similar activity to the compounds of the invention are already known, it appears that in the present case an inventive step could be acknowledged at best only for specific compounds or for a small general class of molecules.

3.2- Having regard to the compounds of formula (I)(3) (tricyclic compounds) the documents D17-D20 are considered the closest prior art. In respect of the compounds

of formula (I)(2) (R4 and R5 form a double bond) the closest prior art is represented by D21. All these documents disclose compounds active on the central nervous system and used for example as anxiolytic. The present compounds (I)(3) and (I)(2) differ from these compounds mainly for the substituent on the free carbon atom of the benzodiazepine ring (group  $(X)_n(Y)_mCOOR1$ ). However, considering the compounds known from the prior art, it appears that this particular moiety (group  $(X)_n(Y)_mCOOR1$ ) is commonly present in this position of the benzodiazepine ring. Accordingly it seems that the skilled person would consider obvious to prepare the compounds of formula (I)(2) and (I)(3) in order to provide further agents having the activity indicated in the present claims 24-26.

Accordingly, in order to acknowledge an inventive step, it should be shown, preferably by means of comparative tests, that the compounds of the invention have unexpected effect vis-à-vis of the compounds of the prior art.

In order to have significative data, the compounds of formula (I)(2) should be compared with the compounds of D21 and the compounds of formula (I)(3) with the compounds of D17-20.

3.3- In addition to the above remarks, it is pointed out that the property establishing an inventive step must extend to the whole of the scope claimed. In this context it is also observed that the possible generalisations of the activity shown for specific compounds should extend only to those variants being obvious modifications and equivalents of the compounds tested. The non-limitative definitions used in the claims such as alkyl, aryl, heteroaryl, aralkyl, heteroaralkyl and dialkylaminoalkyl are in any case not suited to this end.

#### 4- Industrial Applicability

Claims 24-26 relate to subject matter considered by this Authority to be covered by the provisions of Rule 67.1 (iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject matter of this claim, cf. Article 34(4)(a)(i) PCT.

#### Re Item VII

#### **Certain defects in the international application**

1- To meet the requirements of Rule 5.1(a)(ii) PCT, the relevant background art

**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT - SEPARATE SHEET**

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International application No. PCT/US00/13134

disclosed in the cited documents should be identified and the relevant background art disclosed therein should be briefly discussed.

2- The reason for the proviso found in present claim 1 should be explained.

**Re Item VIII**

**Certain observations on the international application**

1- In claim 13 the sentence "R3 is 2-fluorophenyl" should probably read "R2 is 2-fluorophenyl".

However it is observed that claims 13 and 14 appear identical.

2- In claim 27 the functional definition "suitable Michael acceptor" appears as an attempt to define the subject matter in terms of a desired property instead of indicating precisely the technical features (i.e. the chemical structure) specifically designed to solve the problem and thus does not fulfil the requirements of Art. 6 PCT.

# PCT

## REQUEST

The undersigned requests that the present international application be processed according to the Patent Cooperation Treaty.

For rec Office use only

International Application No.

International Filing Date

Name of receiving Office and "PCT International Application"

Applicant's or agent's file reference  
(if desired) (12 characters maximum) PU3318WO

**Box No. I TITLE OF INVENTION**  
SHORT-ACTING BENZODIAZEPINES

**Box No. II APPLICANT**

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)

Glaxo Group Limited  
Glaxo Wellcome House  
Berkeley Avenue  
Greenford, Middlesex  
UB6 ONN  
GB

☐ This person is also inventor.

Telephone No.  
919-483-2370(US number)

Facsimile No.  
919-483-7988(US number)

Teleprinter No.

State (that is, country) of nationality:  
GB

State (that is, country) of residence:  
GB

This person is applicant for the purposes of: ☐ all designated States ☒ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box

**Box No. III FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(S)**

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)

FELDMAN, Paul L.  
c/o Glaxo Wellcome Inc.  
Five Moore Drive, Po Box 13398  
Research Triangle Park, NC 27709  
US

This person is:

☐ applicant only

☒ applicant and inventor

☐ inventor only (If this check-box is marked, do not fill in below.)

State (that is, country) of nationality:  
US

State (that is, country) of residence:  
US

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box

☒ Further applicants and/or (further) inventors are indicated on a continuation sheet.

**Box No. IV AGENT OR COMMON REPRESENTATIVE; OR ADDRESS FOR CORRESPONDENCE**

The person identified below is hereby/has been appointed to act on behalf of the applicant(s) before the competent International Authorities as:

☒ agent ☐ common representative

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)

LEVY, David J.; DADSWELL, Charles E.; GRASSLER, Frank P.; BRINK, Robert H.;  
RIEK, James P.; PRUS, Karen L.; SELBY, Elizabeth; MORGAN, Lorie Ann;  
BENNETT, Virginia C.; ROGERS, Christopher P.; LEMANOWICZ, John L.;  
DEPPENBROCK, Bonnie L.; all of Glaxo Wellcome Inc., Five Moore Drive, PO Box  
13398, Research Triangle Park, NC 27709-3398, US

Telephone No.  
919-483-2370

Facsimile No.  
919-483-7988

Teleprinter No.

☐ Address for correspondence: Mark this check-box where no agent or common representative is/has been appointed and the space above is used instead to indicate a special address to which correspondence should be sent.

**EXPRESS MAIL NO.**  
**EL395943235US**

**C ntinuation f Box N . III FURTHER APPLICANTS AND/OR (FURTHER) INVENTOR(S)**

*If none of the following sub-boxes is used, this sheet is not to be included in the request.*

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)

JUNG, David Kendall  
c/o Glaxo Wellcome Inc.  
Five Moore Drive, PO Box 13398  
Research Triangle Park, NC 27709  
US

This person is:

- ☐ applicant only  
☒ applicant and inventor  
☐ inventor only (If this check-box is marked, do not fill in below.)

State (that is, country) of nationality:  
US

State (that is, country) of residence:  
US

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)

KALDOR, Istvan  
c/o Glaxo Wellcome Inc.  
Five Moore Drive, PO Box 13398  
Research Triangle Park, NC 27709  
US

This person is:

- ☐ applicant only  
☒ applicant and inventor  
☐ inventor only (If this check-box is marked, do not fill in below.)

State (that is, country) of nationality:  
HU

State (that is, country) of residence:  
US

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)

PACOFISKY, Gregory J.  
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Five Moore Drive, PO Box 13398  
Research Triangle Park, NC 27709  
US

This person is:

- ☐ applicant only  
☒ applicant and inventor  
☐ inventor only (If this check-box is marked, do not fill in below.)

State (that is, country) of nationality:  
US

State (that is, country) of residence:  
US

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)

STAFFORD, Jeffrey A.  
c/o Glaxo Wellcome Inc.  
Five Moore Drive, PO Box 13398  
Research Triangle Park, NC 27709  
US

This person is:

- ☐ applicant only  
☒ applicant and inventor  
☐ inventor only (If this check-box is marked, do not fill in below.)

State (that is, country) of nationality:  
US

State (that is, country) of residence:  
US

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box

☒ Further applicants and/or (further) inventors are indicated on another continuation sheet.

## Continuation of Form PCT/RO/101 (continued) III FURTHER APPLICANTS AND/OR (FURTHER) INVENTOR(S)

*If none of the following sub-boxes is used, this sheet is not to be included in the request.*

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)

TIDWELL, Jeffrey H.  
c/o Glaxo Wellcome Inc.  
Five Moore Drive, PO Box 13398  
Research Triangle Park, NC 27709  
US

This person is:

- ☐ applicant only  
☒ applicant and inventor  
☐ inventor only (If this check-box is marked, do not fill in below.)

State (that is, country) of nationality:  
US

State (that is, country) of residence:  
US

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)

This person is:

- ☐ applicant only  
☐ applicant and inventor  
☐ inventor only (If this check-box is marked, do not fill in below.)

State (that is, country) of nationality:

State (that is, country) of residence:

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)

This person is:

- ☐ applicant only  
☐ applicant and inventor  
☐ inventor only (If this check-box is marked, do not fill in below.)

State (that is, country) of nationality:

State (that is, country) of residence:

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)

This person is:

- ☐ applicant only  
☐ applicant and inventor  
☐ inventor only (If this check-box is marked, do not fill in below.)

State (that is, country) of nationality:

State (that is, country) of residence:

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box

☐ Further applicants and/or (further) inventors are indicated on another continuation sheet.

**Box No.V DESIGNATION OF STATE**

The following designations are hereby made under Rule 4.9(a) (*mark the applicable check-boxes; at least one must be marked*):

**Regional Patent**

- ☒ **AP ARIPO Patent:** GH Ghana, GM Gambia, KE Kenya, LS Lesotho, MW Malawi, SD Sudan, SL Sierra Leone, SZ Swaziland, TZ United Republic of Tanzania, UG Uganda, ZW Zimbabwe, and any other State which is a Contracting State of the Harare Protocol and of the PCT
- ☒ **EA Eurasian Patent:** AM Armenia, AZ Azerbaijan, BY Belarus, KG Kyrgyzstan, KZ Kazakhstan, MD Republic of Moldova, RU Russian Federation, TJ Tajikistan, TM Turkmenistan, and any other State which is a Contracting State of the Eurasian
- ☒ **EP European Patent:** AT Austria, BE Belgium, CH and LI Switzerland and Liechtenstein, CY Cyprus, DE Germany, DK Denmark, ES Spain, FI Finland, FR France, GB United Kingdom, GR Greece, IE Ireland, IT Italy, LU Luxembourg, MC Monaco, NL Netherlands, PT Portugal, SE Sweden, and any other State which is a Contracting State of the European Patent Convention and of the PCT
- ☒ **OA OAPI Patent:** BF Burkina Faso, BJ Benin, CF Central African Republic, CG Congo, CI Côte d'Ivoire, CM Cameroon, GA Gabon, GN Guinea, GW Guinea-Bissau, ML Mali, MR Mauritania, NE Niger, SN Senegal, TD Chad, TG Togo, and any other State which is a member State of OAPI and a Contracting State of the PCT (*if other kind of protection or treatment desired, specify on dotted line*)

**National Patent (*if other kind of protection or treatment desired, specify on dotted line*):**

- |  |  |
|--|--|
| <input checked="" type="checkbox"/> AE United Arab Emirates                  | <input checked="" type="checkbox"/> LR Liberia   |
| <input checked="" type="checkbox"/> AL Albania                               | <input checked="" type="checkbox"/> LS Lesotho   |
| <input checked="" type="checkbox"/> AM Armenia                               | <input checked="" type="checkbox"/> LT Lithuania   |
| <input checked="" type="checkbox"/> AT Austria                               | <input checked="" type="checkbox"/> LU Luxembourg  |
| <input checked="" type="checkbox"/> AU Australia                             | <input checked="" type="checkbox"/> LV Latvia  |
| <input checked="" type="checkbox"/> AZ Azerbaijan                            | <input checked="" type="checkbox"/> MA Morocco   |
| <input checked="" type="checkbox"/> BA Bosnia and Herzegovina                | <input checked="" type="checkbox"/> MD Republic of Moldova   |
| <input checked="" type="checkbox"/> BB Barbados                              | <input checked="" type="checkbox"/> MG Madagascar  |
| <input checked="" type="checkbox"/> BG Bulgaria                              | <input checked="" type="checkbox"/> MK The former Yugoslav Republic of Macedonia                             |
| <input checked="" type="checkbox"/> BR Brazil                                |  |
| <input checked="" type="checkbox"/> BY Belarus                               | <input checked="" type="checkbox"/> MN Mongolia  |
| <input checked="" type="checkbox"/> CA Canada                                | <input checked="" type="checkbox"/> MW Malawi  |
| <input checked="" type="checkbox"/> CH and LI Switzerland and Liechtenstein  | <input checked="" type="checkbox"/> MX Mexico  |
| <input checked="" type="checkbox"/> CN China                                 | <input checked="" type="checkbox"/> NO Norway  |
| <input checked="" type="checkbox"/> CR Costa Rica                            | <input checked="" type="checkbox"/> NZ New Zealand   |
| <input checked="" type="checkbox"/> CU Cuba                                  | <input checked="" type="checkbox"/> PL Poland  |
| <input checked="" type="checkbox"/> CZ Czech Republic                        | <input checked="" type="checkbox"/> PT Portugal  |
| <input checked="" type="checkbox"/> DE Germany                               | <input checked="" type="checkbox"/> RO Romania   |
| <input checked="" type="checkbox"/> DK Denmark                               | <input checked="" type="checkbox"/> RU Russian Federation  |
| <input checked="" type="checkbox"/> DM Dominica                              | <input checked="" type="checkbox"/> SD Sudan   |
| <input checked="" type="checkbox"/> EE Estonia                               | <input checked="" type="checkbox"/> SE Sweden  |
| <input checked="" type="checkbox"/> ES Spain                                 | <input checked="" type="checkbox"/> SG Singapore   |
| <input checked="" type="checkbox"/> FI Finland                               | <input checked="" type="checkbox"/> SI Slovenia  |
| <input checked="" type="checkbox"/> GB United Kingdom                        | <input checked="" type="checkbox"/> SK Slovakia  |
| <input checked="" type="checkbox"/> GD Grenada                               | <input checked="" type="checkbox"/> SL Sierra Leone  |
| <input checked="" type="checkbox"/> GE Georgia                               | <input checked="" type="checkbox"/> TJ Tajikistan  |
| <input checked="" type="checkbox"/> GH Ghana                                 | <input checked="" type="checkbox"/> TM Turkmenistan  |
| <input checked="" type="checkbox"/> GM Gambia                                | <input checked="" type="checkbox"/> TR Turkey  |
| <input checked="" type="checkbox"/> HR Croatia                               | <input checked="" type="checkbox"/> TT Trinidad and Tobago   |
| <input checked="" type="checkbox"/> HU Hungary                               | <input checked="" type="checkbox"/> TZ United Republic of Tanzania   |
| <input checked="" type="checkbox"/> ID Indonesia                             | <input checked="" type="checkbox"/> UA Ukraine   |
| <input checked="" type="checkbox"/> IL Israel                                | <input checked="" type="checkbox"/> UG Uganda  |
| <input checked="" type="checkbox"/> IN India                                 | <input checked="" type="checkbox"/> US United States of America Continuation - in- part                      |
| <input checked="" type="checkbox"/> IS Iceland                               |  |
| <input checked="" type="checkbox"/> JP Japan                                 | <input checked="" type="checkbox"/> UZ Uzbekistan  |
| <input checked="" type="checkbox"/> KE Kenya                                 | <input checked="" type="checkbox"/> VN Viet Nam  |
| <input checked="" type="checkbox"/> KG Kyrgyzstan                            | <input checked="" type="checkbox"/> YU Yugoslavia  |
| <input checked="" type="checkbox"/> KP Democratic People's Republic of Korea | <input checked="" type="checkbox"/> ZA South Africa  |
|  | <input checked="" type="checkbox"/> ZW Zimbabwe  |
| <input checked="" type="checkbox"/> KR Republic of Korea                     | Check-boxes reserved for designating States which have become party to the PCT after issuance of this sheet: |
| <input checked="" type="checkbox"/> KZ Kazakhstan                            | <input checked="" type="checkbox"/> DZ Algeria   |
| <input checked="" type="checkbox"/> LC Saint Lucia                           | <input checked="" type="checkbox"/> AG Antigua and Barbuda   |
| <input checked="" type="checkbox"/> LK Sri Lanka                             |  |

**Precautionary Designation Statement:** In addition to the designations made above, the applicant also makes under Rule 4.9(b) all other designations which would be permitted under the PCT except any designation(s) indicated in the Supplemental Box as being excluded from the scope of this statement. The applicant declares that those additional designations are subject to confirmation and that any designation which is not confirmed before the expiration of 15 months from the priority date is to be regarded as withdrawn by the applicant at the expiration of that time limit. (*Confirmation (including fees) must reach the receiving Office within the 15-month time*)

**Supplemental Box** *If the Supplemental Box is not used, this sheet need not be included in the request.*

1. *If, in any of the Boxes, the space is insufficient to furnish all the information: in such case, write "Continuation of Box No. ..." [indicate the number of the Box] and furnish the information in the same manner as required according to the captions of the Box in which the space was insufficient, in particular:*

- (i) *if more than two persons are involved as applicants and/or inventors and no "continuation sheet" is available: in such case, write "Continuation of Box No. III" and indicate for each additional person the same type of information as required in Box No. III. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below;*
- (ii) *if, in Box No. II or in any of the sub-boxes of Box No. III, the indication "the States indicated in the Supplemental Box" is checked: in such case, write "Continuation of Box No. II" or "Continuation of Box No. III" or "Continuation of Boxes No. II and No. III" (as the case may be), indicate the name of the applicant(s) involved and, next to (each) such name, the State(s) (and/or, where applicable, ARIPO, Eurasian, European or OAPI patent) for the purposes of which the named person is applicant;*
- (iii) *if, in Box No. II or in any of the sub-boxes of Box No. III, the inventor or the inventor/applicant is not inventor for the purposes of all designated States or for the purposes of the United States of America: in such case, write "Continuation of Box No. II" or "Continuation of Box No. III" or "Continuation of Boxes No. II and No. III" (as the case may be), indicate the name of the inventor(s) and, next to (each) such name, the State(s) (and/or, where applicable, ARIPO, Eurasian, European or OAPI patent) for the purposes of which the named person is inventor;*
- (iv) *if, in addition to the agent(s) indicated in Box IV, there are further agents: in such case, write "Continuation of Box No. IV" and indicate for each further agent the same type of information as required in Box No. IV;*
- (v) *if, in Box No. V, the name of any State (or OAPI) is accompanied by the indication "patent of addition," or "certificate of addition," or if, in Box No. V, the name of the United States of America is accompanied by an indication "continuation" or "continuation-in-part": in such case, write "Continuation of Box No. V" and the name of each State involved (or OAPI), and after the name of each such State (or OAPI), the number of the parent title or parent application and the date of grant of the parent title or filing of the parent application;*
- (vi) *if, in Box No. VI, there are more than three earlier applications whose priority is claimed: in such case, write "Continuation of Box No. VI" and indicate for each additional earlier application the same type of information as required in Box No. VI;*
- (vii) *if, in Box No. VI, the earlier application is an ARIPO application: in such case, write "Continuation of Box No. VI", specify the number of the item corresponding to that earlier application and indicate at least one country party to the Paris Convention for the Protection of Industrial Property or one Member of the World Trade Organization for which that earlier application was filed.*

2. *If, with regard to the precautionary designation statement contained in Box No. V, the applicant wishes to exclude any State(s) from the scope of that statement: in such case, write "Designation(s) excluded from precautionary designation statement" and indicate the name or two-letter code of each State so excluded.*

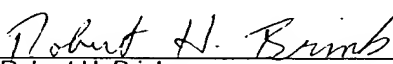
3. *If the applicant claims, in respect of any designated Office, the benefits of provisions of the national law concerning non-prejudicial disclosures or exceptions to lack of novelty: in such case, write "Statement concerning non-prejudicial disclosures or exceptions to lack of novelty" and furnish that statement below.*

**Continuation of BOX IV**

HESKETH, Alan; CRAWLEY, Karen; DOLTON, Peter I.; DAWSON, Hugh; FILLER, Wendy; HACKETT, Ruth; HAMMETT, Audrey; HOCKLEY, Sian Catherine; LANE, Graham; LEAROYD, Stephanie; QUILLIN, Helen; REED, Michael; REES, Marion; STOTT, Mike; TEUTEN, Andrew; THORNLEY, Rachel; VOLCKMAN, Janis; FISHER, Christiane; Elizabeth; all c/o Glaxo Holdings p.l.c., Glaxo House, Berkeley Avenue, Greenford, Middlesex, UB6 ONN, GB

**Continuation of BOX V**

United Kingdom; GB 9911152.8; 14 May 1999(14/05/1999)

<b>Box No. VI PRIORITY CLAIM</b>					<input type="checkbox"/> Further priority claims are indicated in the Supplemental Box.				
Filing date of earlier application (day/month/year)		Number of earlier application		Where earlier application is:					
				national application: country		regional application: regional Office		international application: receiving Office	
item (1) 14/5/1999 14 May 1999		GB 9911152.8		GB					
item (2)									
item (3)									
<input type="checkbox"/> The receiving Office is requested to prepare and transmit to the International Bureau a certified copy of the earlier application(s) (only if the earlier application was filed with the Office which for the purposes of the present international application is the receiving Office) identified above as item(s): _____ <small>* Where the earlier application is an ARIPO application, it is mandatory to indicate in the Supplemental Box at least one country party to the Paris Convention for the Protection of Industrial Property for which that earlier application was filed (Rule 4.10(b)(ii)). See Supplemental Box.</small>									
<b>Box No. VII INTERNATIONAL SEARCHING AUTHORITY</b>									
Choice of International Searching Authority (ISA) (if two or more International Searching Authorities are competent to carry out the international search, indicate the Authority chosen; the two-letter code may be used):					Request to use results of earlier search; reference to that search (if an earlier search has been carried out by or requested from the International Searching Authority): Date (day/month/year)      Number      Country (or regional Office)				
ISA/EP									
<b>Box No. VIII CHECK LIST: LANGUAGE OF FILING</b>									
This international application contains the following number of sheets:  request : 6 description (excluding sequence listing part) : 75 claims : 13 abstract : 1 drawings : sequence listing part of description : Total number of sheets : 95					This international application is accompanied by the item(s) marked below: 1. <input checked="" type="checkbox"/> fee calculation sheet 2. <input checked="" type="checkbox"/> separate signed power of attorney 3. <input type="checkbox"/> copy of general power of attorney; reference number, if any: 4. <input type="checkbox"/> statement explaining lack of signature 5. <input checked="" type="checkbox"/> priority document(s) identified in Box No. VI as item(s): (1) 6. <input type="checkbox"/> translation of international application into (language): 7. <input type="checkbox"/> separate indications concerning deposited microorganism or other biological material 8. <input type="checkbox"/> nucleotide and/or amino acid sequence listing in computer readable form 9. <input checked="" type="checkbox"/> other (specify): Resolution				
Figure of the drawings which should accompany the abstract:					Language of filing of the international application: ENGLISH				
<b>Box No. IX SIGNATURE OF APPLICANT OR AGENT</b>									
Next to each signature, indicate the name of the person signing and the capacity in which the person signs (if such capacity is not obvious from reading the request).  <div style="text-align: center;">             Robert H. Brink            Attorney of Record         </div>									

For receiving Office use only			
1. Date of actual receipt of the purported international application:		2. Drawings:  <input type="checkbox"/> received:  <input type="checkbox"/> not received:	
3. Corrected date of actual receipt due to later but timely received papers or drawings completing the purported international application:			
4. Date of timely receipt of the required corrections under PCT Article 11(2):			
5. International Searching Authority (if two or more are competent): ISA/		6. <input type="checkbox"/> Transmittal of search copy delayed until search fee is paid.	

For International Bureau use only	
Date of receipt of the record copy by the International Bureau:	